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The effect of maximum tumor diameter and 18F-FDG PET/CT imaging status on overall survival in Hodgkin lymphoma patients

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ABSTRACT

Aims: This research aims to determine the impact of maximum tumor diameter and FDG PET CT status at the time of diagnosis on survival outcomes and to identify prognostic factors that influence treatment response and survival.

Methods: 239 patients with a diagnosis of Hodgkin lymphoma participated in the study. Clinical characteristics, treatment responses, and prognostic factors influencing survival were retrospectively analyzed from patient medical records.

Results: There were 136 (56.9%) male patients and 103 (43.1%) female patients, who participated in the study. Of these patients, 202 (84.5%) survived, while 37 (15.5%) died during the study period. When surviving patients and non-survivor patients were compared, the deceased patients had a higher mean age (p=0.003), a higher prevalence of spleen involvement and B symptoms (p=0.011 and p=0.001, respectively), lower albumin levels (p=0.008), higher beta-2 microglobulin levels (p=0.001), and more bone marrow involvement (p=0.006). A fourfold increase in mortality was seen in patients with beta-2 microglobulin levels >2920 mg/L, and a 3.188-fold increase in mortality was seen in patients with spleen involvement.

Conclusion: In conclusion, beta-2 microglobulin >2920 mg/L, the presence of spleen involvement, the presence of relapse, and the presence of progressive or refractory disease in FDG PET CT were significant prognostic factors for 1st, 3rd, and 5th-year survival rates in patients with Hodgkin lymphoma. In addition, there was no correlation between survival rate and maximum tumor diameter as measured by FDG-PET or CT.

Keywords: Hodgkin lymphoma, clinical indicators, prognostic factors, FDG PET CT

INTRODUCTION

Hodgkin lymphoma (HL) is a B-cell lymphoma that accounts for 10%-15% of all lymphomas. It has a bimodal age distribution in the 3rd and 6th decades. HL is one of the most common malignancies in young adults and one of the best-treated cancers, with a cure rate of 90%.[1,2] Current treatment options for HL include chemotherapy and radiotherapy regimens, depending on the stage of the disease. A high cure rate in early-stage Hodgkin lymphoma (HL) is a big step forward in hemato-oncology.[3] But late side effects of treatment may put long-term disease free survival (DFS) and health at risk.[4] Individualized approaches to treatment become more important. [18F]-fluorodeoxy-D-glucose positron emission tomography (FDG-PET/CT) is an imaging system that can be used to demonstrate the metabolic activity of a tumor. Therefore, it is used to evaluate the response to treatment during HL treatment. As one of the first applications of personalized medicine, PET-guided approaches have been tested and successfully implemented in HL clinical practice. FDG-PET/CT is commonly used to monitor treatment response in HL patients. In HL, the early treatment response measured by [18F]-fluorodeoxyglucose (FDG) positron emission tomography (PET) has become a potent indicator of prognosis.[5] Pet-guided treatments in Hodgkin lymphoma have become widely accepted after prospective studies with a large number of patients and a high level of evidence have been conducted on this subject.[6,7] However, the relationship between FDG-PET/CT maximum standardized uptake value (SUVmax) and treatment response or overall survival values is not clear in the literature. For the majority of patients, who achieved a complete

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response following treatment, neither clinical status nor imaging techniques alone accurately predicted disease relapse and survival.[8,9] There is a need for research on additional biomarkers that influence survival and treatment response. In the era of PET-adapted therapy, uncertainty still surrounds the prognostic significance of tumor volume in the HL. Treatment response and disease overall survival in Hodgkin lymphoma patients are thought to be related to maximum tumor diameter and maximum FDG PET-CT SUV uptake at the time of diagnosis.[10,11] The purpose of this study is to assess the prognostic factors influencing treatment response and survival, as well as to demonstrate the effects of maximum tumor diameter and FDG PET CT status at the time of diagnosis on survival outcomes.

METHODS

This retrospective study was carried out with the permission of the Uludağ University Faculty of Medicine Clinical Researches Ethics Committee (Date: 19.02.2020, Decision No: 2020-3/8). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study included 239 patients, who presented to the Adult Hematology Outpatient Clinic between January 2010 and January 2020 with a diagnosis of Hodgkin lymphoma. Patients' archived medical records were retrospectively analyzed for epidemiological information, clinical characteristics, treatment responses, and prognostic factors influencing survival. The birth date, disease onset age, disease duration, clinical findings, and biochemical results of each patient were evaluated. The maximum tumor diameter and SUVmax values at the time of diagnosis were determined by analyzing the system's stored radiological images. Patients with missing information were excluded from the study.

Statistical analysis

SPSS 25.0 (IBM Corporation, Armonk, New York, United States) and Medcalc 14 (Acacialaan 22, B-8400 Ostend, Belgium) programs were used to analyze the variables. The conformity of the data to the normal distribution was evaluated with the Shapiro-Wilk Francia test, while the homogeneity of variance was evaluated with the Levene test. In the comparison of two groups according to quantitative variables, the Mann Whitney U test, one of the non-parametric tests, was tested using Monte Carlo simulation results, while the Independent Two Samples T test, one of the parametric methods, was tested using the Boostrap method. The Pearson Chi-Square, Fisher Exact, and Fisher Freeman Halton tests were used to compare categorical variables using the Monte Carlo Simulation technique.The resulting categorical variables were compared in Kaplan Meier (log rank) analysis. Variables with $p<0.10$ in Kaplan Meier analysis were taken and modeled using the backward elimination method in Cox regression analysis. The variables were analyzed at a 95% confidence level, and a p-value of less than 0.05 was considered significant. Quantitative variables were expressed as mean (standard deviation) and median (minimum/maximum) in the tables, while categorical variables were shown as n (%).

RESULTS

There were 136 (56.9%) male patients and 103 (43.1%) female patients, who reviewed retrospectively. The mean age of the patients was 41.53±15.9. Of the patients, 202 (84.5%) survived, while 37 (15.5%) died during the study period. In total, 126 (55.3%) of the patients had the nodular sclerosis subtype of Hodgkin lymphoma, while 40 (17.5%) had the mixed cellular variant. Only 26 patients (11.1%) had involvement in the spleen and 15 patients (6.5%) had bulky disease. Only 19 (12.8%) of the patients had bone marrow involvement, and only 19 (7.9%) of the patients had comorbidities. Chemotherapy treatment was applied to every patient, but only 26 patients (11.6%) received radiotherapy. **Table 1** shows the regions of lymph node involvement based on FDG-PET CT and CT scans, along with the distribution of clinical status following treatment. The patients participating in the study were receiving similar treatments.

Table 2 shows the findings of the routine blood tests and disease datasets that were performed on the patients. CT analysis confirmed a maximum tumor diameter of 38.93±20.97 millimeters. The patients were monitored for a total of 69.12±44.25 months during the follow-up period. When the surviving patients and the patients who died were compared, the dead patients had a higher mean age (p=0.003), a greater prevalence of spleen involvement and B symptoms (p=0.011 and p=0.001, respectively), lower albumin levels (p=0.008), higher beta-2 microglobulin levels (p=0.001), and greater bone marrow involvement (p=0.006). In addition, the deceased patients had a lower mean albumin level In addition, the FDG PET CT evaluation after treatment revealed significant differences between the two groups in terms of the progression or refractoriness of the disease, as well as partial and complete response. There was no statistical difference between maximum tumor diameter in FDG PET CT or CT (**Table 3**).

Table 1. Baseline characteristics of patients with Hodgkin lymphoma

	n (%)
Mortality	
Alive	202 (84.5)
Exitus	37 (15.5)
Gender	
Male	136 (56.9)
Female	103 (43.1)
Hodgkin Lymphoma Subtype	
Lymphocyte-Rich	15 (6.6)
Nodular Sclerosis	126 (55.3)
Classical	33 (14.5)
Mix Cellular	40 (17.5)
Nodular Lymphocyte Predominant	11 (4.8)
Lymphocyte Depleted	3 (1.3)
Extralymphatic involvement	
Absent	209 (88.9)
Present	26 (11.1)
Spleen involvement	
Absent	193 (83.5)
Present	38 (16.5)
Bulky Disease	
Absent	216 (93.5)
Present	15 (6.5)
B Symptoms	
Absent	127 (55)
Present	104 (45)
Co-morbidity	
Absent	220 (92.1)
Present	19 (7.9)
Major involvement region in PET-CT	
Cervical region	54 (46.6)
Mediastinum	40 (34.5)
Abdominal	5 (4.3)
Pelvic and inguinal	7 (6)
Bone	2 (1.7)
Axilla	8 (6.9)
Major involvement region in CT	
Cervical region	40 (49.4)
Mediastinum	19 (23.5)
Abdominal	8 (9.9)
Pelvic and inguinal	10 (12.3)
Axilla	4 (4.9)
Bone marrow involvement	
Absent	130 (87.2)
Present	19 (12.8)
Radiotherapy	
Not performed	198 (88.4)
Performed	26 (11.6)
PET-CT Results after treatment	
Progressive or refractory disease	25 (11.4)
Partial response	5 (2.3)
Complete response	188 (85.5)
Unknown	2 (0.9)
Relapse	
Present	66 (30.6)
Absent	150 (69.4)

Table 2. Blood routine examination and disases indexes of patients with Hodgkin lymphoma

	Mean (SD.)	Median (min-max)
Age	41.53 (15.9)	39 (18-82)
White blood cell	10569.97 (6511.93)	9140 (1100-38800)
Lymphocyte	2114.01 (1452.76)	1910 (207-17700)
Monocyte	739.35 (475.65)	616 (10-3520)
Hemoglobin	12.23 (2.05)	12.3 (5.7-17.6)
Albumin g/dl	4.05 (0.51)	4.15 (2-5.1)
Lactate dehydrogenase	229.74 (84.72)	204 (118-587)
Beta 2 microglobulin	2382.9 (1237.27)	2011 (702-8330)
Erythrocyte sedimentation rate	44.48 (32.24)	38 (2-120)
Creatinin	0.76 (0.27)	0.71 (0.4-3.6)
Maximum tumor diameter in FDG PET CT	37.08 (30.46)	18.9 (10.2-99)
Maximum tumor diameter in CT	38.93 (20.97)	31 (13-130)
Chemotherapy session count	6.33 (1.78)	6 (2-12)
Follow up duration (Month)	69.12 (44.25)	67 (1-364)

SD.:Standart deviation, min:minimum, max: Maximum

The cut-off values were determined between the statistically significant numerical values (age, beta-2 microglobulin, albumin) between both groups. These cut-off values were >47 for age, 2920 mg/L for beta-2 microglobulin, and 3.6 for albumin. Considering the diagnostic accuracy of these cut-off values, it was 0.647 for albumin for age and 0.649 for beta-2 microglobulin (AUC). (**Table 4**). **Table 5** provides an analysis of survival based on patient and disease variables. Age ≤47 years, an albumin value >3.6, beta-2 microglobulin values ≤2920 mg/L, absence of spleen, the absence of B symptoms, the absence of bone marrow involvement, the presence of a complete response, and the absence of relapse were statistically associated with increased life expectancy. The stages of the patients were examined at the time of diagnosis. At the time of diagnosis, the stages were evaluated as favorable, unfavorable and advanced. The survival rate of patients in the advanced stage was significantly lower. (p <0.001). Those with beta-2 microglobulin levels >2920 mg/L had a fourfold higher mortality rate than those with beta-2 microglobulin levels greater than >2920 mg/L. Those with spleen involvement had a 3.188-fold higher mortality rate. The mortality odds ratio for each subgroup appeared to be less than one at the end of the treatment period, indicating a protective factor. When compared to those who progress, those who had a complete response after treatment had a 7.8 times higher mortality rate (**Table 6**).

Table 3. The effect of the disease and patients' charecteristics in terms of living status

	Alive (n=202)	Exitus (n=37)	p
Age, median (min/max)	36.5 (18/82)	50 (19/79)	0.003[u]
Gender (Female), n (%)	90 (44.6)	13 (35.1)	0.367[c]
Hodgkin lymphomca subtype, n (%)			0.943[ff]
Lymphocyte-Rich	14 (7.3)	1 (2.7)	
Nodular Sclerosis	104 (54.5)	22 (59.5)	
Classical	28 (14.7)	5 (13.5)	
Mix Cellular	33 (17.3)	7 (18.9)	
Nodular lymphoycte predominant	9 (4.7)	2 (5.4)	
Lymphocye Depleted	3 (1.6)	0 (0)	
Presence of extralymphatic involvement,n(%)	20 (10)	6 (17.6)	0.232[f]
Presence of spleen involvement, n (%)	27 (13.7)	11 (32.4)	0.011[c]
Presence of Bulky Mass, n (%)	13 (6.6)	2 (5.9)	0.999[f]
Presence of B symptoms, n (%)	80 (40.6)	24 (70.6)	0.001[c]
Iliac and inguinal lymph node involvement , n (%)			0.553[ff]
Absent	168 (85.3)	29 (85.3)	
Iliac and inguinal lymph node involvement	6 (3)	2 (5.9)	
Iliac involvement	8 (4.1)	0 (0)	
Inguinal involvement	15 (7.6)	3 (8.8)	
Co-morbidity, n (%)	15 (7.4)	4 (10.8)	0.507[f]
White blood cell count, median (min/max)	9085 (1380/38800)	10300 (1100/27280)	0.734[u]
Lymphocyte, median (min/max)	1910 (277/17700)	1830 (207/6180)	0.584[u]
Monocyte, median (min/max)	607 (10/3520)	661.5 (177/1840)	0.598[u]
Hemoglobin, mean (SD.)	12.3 (2.08)	11.84 (1.78)	0.215[t]
Albumin, median (min/max)	4.2 (2/5.1)	4 (2.4/4.6)	0.008[u]
Lactate dehydrogenase, median (min/max)	202.5 (118/587)	216 (153/549)	0.193[u]
Beta 2-microglobulin, median (min/max)	1948.5 (702/8330)	3053 (1323/5206)	0.001[u]
Eritrocyte sedimantation rate, median (min/max)	39 (2/120)	32.5 (2/105)	0.597[u]
Creatinin, median (min/max)	0.7 (0.4/2.11)	0.79 (0.49/3.6)	0.217[u]
Max tumor diameter in FDG PET CT (mm), median (min/max)	18.1 (10.2/99)	25 (11/98)	0.383[u]
Max tumor diameter inCT (mm), median (min/max)	31.5 (15/130)	28 (13/100)	0.688[u]
Bone marrow involvement, n (%)			0.006[f]
Absent	112 (91.1)	18 (69.2)	
Present	11 (8.9)	8 (30.8)	
Chemotherapy session count	6 (2/12)	8 (2/8)	0.107[u]
Radiotherapy administration , n (%)	24 (12.6)	2 (5.9)	0.385[f]
FDG PET CT after treatment, n (%)			0.001[ff]
Progressive/Refractory disease	16 (8.5)	9 (29)	
Partial response	3 (1.6)	2 (6.5)	
Complete response	169 (89.4)	19 (61.3)	
Unknown	1 (0.5)	1 (3.2)	
Relaps presence, n (%)	40 (21.6)	26 (83.9)	<0.001[c]
Systemic Inflamatory Response Index (SIRI)	209.66 (1.02/6679.78)	190.71 (41.83/2239.11)	0.944[u]
Systemic Inflamatory Index (SII)	86.58 (0.04/3473.48)	104.51 (11.84/1638.41)	0.458[u]

[u] Mann Whitney-U Test (Monte Carlo), [c] Chi Square Test (Monte Carlo), [ff] Fisher Freeman Halton Test (Monte Carlo), [f] Fisher Exact Test (Monte Carlo), [t] Independent Two Samples T Test (Boostrap), SD.:Standard Deviation, min: Minimum, max: Maximum

Table 4. Determination of cut-off values for predicting mortality according to Age, Albumin and Beta 2 microglobulin variables

Reference: Exitus	Cut off	Sensitivity	Specificity	+PPV	-PPV	AUC±SE.	P Value
Age	>47	59.46	67.33	25	90.1	0.647±0.054	0.007
Albumin g/dl	≤ 3.6	41.94	85.56	32.5	89.9	0.649±0.053	0.005
Beta 2 Microbulin mg/L	>2920	61.9	85.06	36.1	94.2	0.714±0.068	0.002

ROC (Receiver Operating Curve) Analysis (Honley&Mc Nell-Youden index J), AUC: Area under the ROC curve, SE: Standard Error, +PV: Positive Predictive Value, -PV: Negative Predictive Value

Table 5. Survival analysis results according to patient and disease characteristics

	Alive	Exitus	Estimate Survival	Estimate Proportion Surviving at the	P value
	n (%)	n (%)	Mean±SE.	1/3/5 years	
Age					0.012
≤ 47	136 (67.3)	15 (40.5)	238.021±58.575	97.3/95.9/93.0	
>47	66 (32.7)	22 (59.5)	158.694±13.619	93.1/81.9/75.7	
Albumin					<0.001
>3.6	175 (86.6)	24 (64.9)	206.388±34.623	98.0/96.8/95.6	
≤ 3.6	27 (13.4)	13 (35.1)	91.808±8.645	82.4/49.0/49.0	
Beta 2-microglobulin					<0.001
≤ 2920	131 (64.9)	8 (21.6)	211.92±6.44	100.0/99.2/97.1	
>2920	71 (35.1)	29 (78.4)	175.041±38.526	90.0/80.9/73.6	
Spleen involvement					0.003
Absent	170 (86.3)	23 (67.6)	205.101±34.631	96.9/95.7/93.1	
Present	27 (13.7)	11 (32.4)	110.559±10.346	89.1/61.7/61.7	
B symptoms					0.001
Absent	117 (59.4)	10 (29.4)	269.489±43.624	99.2/97.4/92.8	
Present	80 (40.6)	24 (70.6)	129.626±7.976	92.3/86.5/79.3	
Bone marrow involvement					0.011
Absent	112 (91.1)	18 (69.2)	197.249±7.099	96.1/91.7/86.6	
Present	11 (8.9)	8 (30.8)	95.789±10.608	94.7/89.5/78.3	
FDG PET CT status. after treatment					<0.001
Progressive/Refractory disease	16 (8.5)	9 (29.0)	64.485±8.384	92.0/43.1/43.1	
Partial response	3 (1.6)	2 (6.5)	85.750±25.398	100.0/75.0/50.0	
Complete response	169 (89.4)	19 (61.3)	207.4343±34.451	98.9/98.9/96.1	
Unknown	1 (0.5)	1 (3.2)	60.00±38.891	50.0/50.0/50.0	
Relapse					<0.001
Absent	145 (78.4)	5 (16.1)	346.810±8.012	98.7/98.7/97.7	
Present	40 (21.6)	26 (83.9)	118.919±13.303	92.1/68.2/42.1	
Stages at the diagnosis					0.001
Favorable	50 (25.4)	2 (5.9)	136.957±3.463	100.0/94.0/94.0	
Unfavorable	62 (31.5)	4 (11.8)	152.507±5.017	100.0/90.9/90.9	
Advanced	85 (43.1)	28 (82.4)	170.733±28.986	92.0/87.0/81.1	

Kaplan Meier Test;Log Rank (Mantel-Cox), SE.: Standard Error

Table 6: Cox regression analysis of variables affecting mortality

Independent Variables	B±Sh	p value	Odds Ratio (95% C.I.)
Beta-2 Microglobulin (<2920) mg/L	1.387±0.548	0.011	4.002 [1.368-11.709]
Spleen Involvement	1.159±0.507	0.022	3.188 [1.18-8.614]
PET-CT evaluation after treatment		0,001	
Progressive/Refractory Disease vs Complete response	2.054±0.581	<0.001	7.81 [2.49-24.39]
Partial response vs Complete response	2.401±0.932	0,010	10.99 [1.77-66.66]
Progressive/Refractory Disease vs Partial response	0.347±0.872	0.690	1.41 [0.26-7.81]
Relapse	1.736±0.64	0.007	5.677 [1.62-19.889]
Estimate Proportion Surviving at the 1/3/5 years (Sh.): 99.8 (0.002)/99.0 (0.007)/96.0 (0.019)-Base Line Hazard: 0.325			

Cox Regression-Stepwise (Wald) Model, C.I.: Confidence interval B: regression coefficients SE.: Standard Error

DISCUSSION

In HL, the overall survival rate exceeds 90%.[3,12] These excellent results, however, have the drawback of an increased risk of long-term toxicity as a result of chemotherapy and/or radiation.[4] In addition, 10 to 30 percent of patients are refractory to treatment or experience recurrence. Researchers have identified a number of factors that decrease the survival rate in HL over the past decades.[10] In our study, when the patients, who died during the study, were compared with the patients who survived, the surviving patients were younger, had less spleen involvement and B symptoms, higher albumin values, lower beta-2 microglobulin values, and less bone marrow involvement. Moreover, these variables affect the survival rates of patients in the first, third, and fifth years. In the International Prognostic Score for Hodgkin Lymphoma, being over the age of 45 is scored as unfavorable. In addition, according to the European Organization for Research and Treatment of Cancer (EORTC), being over the age of 50 is considered

unfavorable.[13] In our study, in patients over 47 years of age, 1, 3, and 5 year estimated survival rates were significantly higher than those in patients under ≤47 years of age. Depending on the subtype, the disease characteristics of HL patients can vary significantly. However, it is known that survival rates decline with age. Our findings are consistent with the literature.

In HD, the spleen is usually considered a nodal organ. Rarely does Hodgkin lymphoma affect only the spleen. Splenic involvement is found in 30-40% of HD patients at the time of diagnosis.[14] In the early stages of Hodgkin's lymphoma, the spleen is the organ most often affected by occult disease. The German Hodgkin Lymphoma Study Group looked at 391 patients in limited early clinical stages. In 21% of these, laparotomy found occult abdominal lymphoma, and in 86.6%, the spleen was affected.[15] In our study, in the presence of spleen involvement, the mortality rate was 3.188 times higher. In addition, according to the findings of the German Hodgkin Lymphoma Study Group, involvement of the spleen and bone marrow occurs in advanced stages 3-4 of the disease.[16] In our study, the decrease in survival rates in patients with spleen and bone marrow involvement is consistent with the literature. The German Hodgkin Lymphoma Study Group, and the European Organization for Research and Treatment of Cancer evaluated the presence of B symptoms as unfavorable factors.[17,18] Likewise, in our study, the survival rate was lower in those with B symptoms. Hypoalbuminemia and higher beta-2 microglobulin can be used to determine the disease as unfavorable and may point to the presence of cancer-related inflammation in the body.[19,20] In our study, the mortality rate of patients with beta 2 globulin levels higher than 2920 mg/L was found to be four times higher than that of those with beta 2 globulin levels lower than 2920 mg/L.

PET-CT-based treatment response assessment has recently become a widely accepted method. In spite of the progress that has been made in standardizing the use of PET/CT in lymphoma, there are still challenges to be faced, most notably with regard to the limited positive predictive value.[21] The presence of relapsed or refractory disease following a PET-CT examination results in a significant reduction in survival rates. Tumor mass has long been considered to be prognostic in HL, but uncertainty remains regarding the significance and definition of the mass in the era of PET-adapted evaluation. In addition, the connection between the maximum tumor diameter measured by FDG PET/CT and the patient's likelihood of survival is not yet fully understood. In early-stage HL patients, Illidge et al.[10] demonstrated that there is a correlation between the maximum tumor diameter and both relapse and complete metabolic response. There are also studies that report that the relationship cannot be precisely defined. Existing relapsed or refractory disease after PET-CT examination significantly reduces survival rates. Some studies indicate that the size of the tumor at the time of diagnosis has an effect on survival rates, but other studies say the opposite.[21-23] In our study, there was no association between survival and the maximum diameter value of the tumor as measured by FDG-PET or CT. Furthermore, the location of the tumor with the maximum tumor diameter at the time of diagnosis did not affect survival. The primary limitations of this study may be that the computed tomography and FDG PET CT scans were done by different specialists, there was a lack of standardization in the range widths of the examined image sections, and all Hodgkin lymphoma subtypes were evaluated at once.

CONCLUSION

Beta-2 microglobulin >2920 mg/L , the presence of spleen involvement, the presence of relapse (n;66, 28%, Estimate Survival, Mean±SE.; 118.919±13.303), and having a progressive or refractory disease evaluation after treatment with FDG PET CT were the most relevant independent prognostic factors for the 1st, 2nd, and 5th-year survival rates with Hodgkin's lymphoma patients. In addition, no correlation was detected between the survival rate and the maximum tumor diameter as measured by FDG-PET or CT.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Uludağ University Faculty of Medicine Clinical Researches Ethics Committee (Date: 19.02.2020, Decision No: 2020-3/8).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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